



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,155	01/12/2004	James McSwiggen	MBHB02-742-N (400/141)	5758
20306	7590	02/22/2006	EXAMINER	
MCDONNELL BOEHNNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606				
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

1. Applicant's election of the target group that is both VEGFR1 and VEGFR2 (see pg. 3 of the requirement for restriction mailed 10/27/05) by amendment of the instant claims to read only on the target group that is both VEGFR1 and VEGFR2 including cancellation of all claims drawn to single target groups that are either VEGFR1 or VEGFR2, in the reply filed 11/28/05, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Application

2. Claims 1-3, 10-24, 32 and 35 are pending in this application. Claims 4-9, 25-31 and 33-34 were cancelled by Applicant in the reply filed 11/28/2005.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application claims the benefit of priority of an earlier filing date to a number of continuation in part provisional and non-provisional and PCT/ international application(s). A review of the prior-filed applications fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application prior to the filing of PCT US03/05022. In particular, no disclosure could be located in the priority documents as claimed, of the instantly claimed double stranded nucleic acid (dsNA) molecules comprising sense and antisense strands that are each independently of a range of about 19 to about 29 nucleotides in length. If Applicant believes that a disclosure of the instantly claimed length range of dsNAs is to be found in the claimed priority documents, Applicant should point out, with particularity, where such support is to be found.

Therefore, the effective filing date of instant claims 1-3, 10-24, 32 and 35 is considered to be the filing date of PCT US03/05022, which is 02/20/2003.

Information Disclosure Statement

4. Certain references on the information disclosure statement filed 7/22/2004 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because they are incomplete references or because they lack dates. The IDS has been placed in the application file, but certain references (see pgs. 8, 9 and 14-16) have not been considered as to the merits. Applicant is advised that the date of any re-submission of

Art Unit: 1635

any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

5. Claim 1 is objected to because of the following informalities: Claim 1 ends in a “.”. Appropriate correction is required.
6. Claim 35 is objected to because of the following informalities: Claim 35 recites, “in pharmaceutically acceptable carrier.” but was probably intended to recite. “in a pharmaceutically acceptable carrier.”. Appropriate correction is required.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

Art Unit: 1635

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-3, 10-24, 32 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 10/664,668 and claims 49-51 and 58-76 of copending Application No. 10/444,853. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Instant claims 1-3, 10-24, 32 and 35 are drawn to a chemically synthesized double stranded nucleic acid molecule comprising a sense and an antisense strand wherein each strand is independently about 19 to about 29 nucleotides in length and wherein said antisense strand comprises nucleotide sequence that is complementary to nucleic acid sequence encoding VEGFR1 and VEGFR2 or portions thereof. Dependent claims 2-3, 11-24, 32 and 35 require that the claimed dsNA molecule comprise or does not comprise ribonucleotides, wherein the sense and antisense strands are connected by a linker that is a nucleotide or non-nucleotide linker, wherein the pyrimidine or purine residues of the sense or antisense strands comprise particular nucleotide modifications or phosphorothioate internucleoside linkages, wherein the sense or antisense strands comprise terminal cap moieties that can be inverted deoxy abasic moieties or glyceryl moieties and to a composition comprising the claimed dsNA and a pharmaceutically acceptable carrier.

Claims 1-30 of copending Application No. 10/664,668 and claims 49-51 and 58-76 of copending Application No. 10/444,853 are drawn to chemically synthesized double stranded nucleic acids wherein each strand comprises about 19-23 nucleotides wherein the ds nucleic acids are targeted to VEGFR2 or a human gene, respectively. Claims 1-30 of copending Application No. 10/664,668 require that the dsNA claimed comprise at least one chemical modification and claims 49-51 and 58-76 of copending Application No. 10/444,853 require that at least 35% of the internal nucleotides on each strand be modified with sugar modifications that are different from each other. The dependent claims in both copending Applications recite the same limitations as the claims of the instant application and require that the claimed dsNA molecule comprise or does not comprise ribonucleotides, wherein the sense and antisense strands are connected by a linker that is a nucleotide or non-nucleotide linker, wherein the pyrimidine or purine residues of the sense or antisense strands comprise particular nucleotide modifications or phosphorothioate internucleoside linkages, wherein the sense or antisense strands comprise terminal cap moieties that can be inverted deoxy abasic moieties or glyceryl moieties and to a composition comprising the claimed dsNA and a pharmaceutically acceptable carrier.

The claims set forth in each of the above copending Applications are drawn to chemically synthesized double stranded nucleic acid molecules that comprise required nucleobase, internucleoside linkage and sugar modifications that are all well known and routine in the art of nucleic acid therapeutics, with the differences between the instant application and each of the copending applications being the particular nucleotide or

Art Unit: 1635

nucleoside modifications recited in the independent claims. However, as part of the obviousness type double patenting analysis, portions of the instant disclosure which provide support for the claims in the potentially conflicting patent or application can be relied upon in making a rejection. In this case, the specification as filed, discloses each of the nucleotide or nucleoside modifications claimed in each of the copending Applications above and the desirability of making each of these modifications in formulating the nucleic acids of the invention (see pages 12-47 of the specification as filed for an extensive disclosure of double stranded nucleic acid molecules that comprise chemical modifications and that are formulated with in the instantly claimed length range and comprise and do not comprise ribonucleotides, linkers, internucleoside linkages, terminal cap moieties and can be formulated in pharmaceutically acceptable carriers)

Therefore, the instantly claimed compositions and the compositions claimed in the copending Applications above are considered essentially the same, except for the routine nucleotide and nucleoside modifications that are well known in the art (as disclosed in the instant specification) and are reasonably interpreted as being obvious variants over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 10-24, 32 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a chemically synthesized double stranded nucleic acid molecule comprising a sense and an antisense strand wherein each wherein the antisense strand comprises nucleotide sequence that is complementary to nucleic acid sequence encoding VEGFR1 and VEGFR2 or portions thereof. Dependent claims 2-3; 11-24, 32 and 35 require that the claimed dsNA molecule comprise or does not comprise ribonucleotides, wherein the sense and antisense strands are connected by a linker that is a nucleotide or non-nucleotide linker, wherein the pyrimidine or purine residues of the sense or antisense strands comprise particular nucleotide modifications or phosphorothioate internucleoside linkages, wherein the sense or antisense strands comprise terminal cap moieties that can be inverted deoxy abasic moieties or glyceryl moieties and to a composition comprising the claimed dsNA and a pharmaceutically acceptable carrier.

The instant claims are broadly drawn and read on a vast number of dsNA molecules that are complementary to nucleic acid sequence encoding VEGFR1, VEGFR2, VEGFR1 and VEGFR2 or any portions thereof, that will function, (as contemplated in the specification) to inhibit the expression of both VEGFR1 and/or VEGFR2. The claims read on dsNAs, the function of which is to inhibit the expression all nucleic acid sequences that encode VEGFR1 and/or VEGFR2 from any organism and include splice variants, isoforms and alleles of both VEGFR1 and/or VEGFR2 and any portions thereof.

The specification as filed discloses species of dsNA sequences that are 21 sense and antisense nucleotide strands that are complementary over 19 bp, to nucleic acid sequence encoding VEGFR1 and/or VEGFR2 and that comprise 2, 3' terminal thymidine nucleobase residues. The specification discloses no species that are complementary to only a portion of VEGFR1 and/or VEGFR2 that will function to inhibit the expression of both VEGFR1 and VEGFR2, commensurate with the breadth of what is claimed. The specification provides a general disclosure of what is encompassed by dsNAs of the invention including general considerations in terms of structure, chemistry and formulation. However, the specification provides description of dsNAs that comprise nucleotide sequence that is complementary to nucleic acids encoding both VEGFR1 and VEGFR2, or portions thereof, that will function, commensurate with the breadth of what is claimed, to inhibit the expression of both genes.

The general disclosure of the specification, therefore, fails to provide an adequate written description of the broad genus of compounds as claimed because the

Art Unit: 1635

specification does not provide a representative number of species of the claimed compounds. Additionally, the specification as filed has not disclosed any distinguishing identifying characteristics of the broad genus of compounds as claimed, that would indicate that Applicant was in possession of this broad genus, commensurate with the breadth of what is claimed.

The specification does provide a description of the claimed dsNA that would reasonably lead one of skill in the art to the instant invention or that would allow the skilled artisan to recognize that Applicant was in possession of the instant invention, commensurate with the breadth of what is claimed and the state of the art cannot provide the required guidance. This is evidenced by Elbashir et al. 2001 (Cited on Form PTO 1449, filed 07/22/2004 in this application) who provide a general outline for the construction of interfering RNAs (siRNAs), pointing out that target recognition is highly sequence specific and that the nucleotide sequence at the target site and/or the accessibility of the target RNA structure may be responsible for variations in silencing efficiency (pg. 6885, col. 2). In view of the state of the art recognition that target gene inhibition utilizing dsRNAs was highly sequence specific, the skilled artisan would not recognize that Applicant was in possession of the invention as claimed.

MPEP § 2163[R-2] I. states:

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); < Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at

Art Unit: 1635

1563-64, 19 USPQ2d at 1117.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of a representative number of species from within the broad genus of compounds now claimed or by describing distinguishing identifying characteristics of the claimed compounds that is sufficient to show that the applicant was in possession of the instant invention, commensurate with the breadth of what is claimed.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

Art Unit: 1635

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-3, 11-24, 32 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Lockridge et al. (US 2003/0216335).

The disclosure of Lockridge et al. is applied as prior art because, although Lockridge et al. is claimed in the instant application for the benefit of a prior-filed application, the disclosure of Lockridge et al. is not considered to provide support a claim to the benefit of priority of an earlier filed document as above. However, although the disclosure of Lockridge et al. (as supported by Provisional Application 60/334,461) does not provide support for the claimed length range of about 19 to about 29 as instantly claimed, the disclosure of Lockridge sets forth particular double stranded nucleic molecules, the length of which fall within the instantly claimed size range and are therefore reasonably considered to anticipate the instant invention.

The invention as set forth in claims 1-3, 11-24, 32 and 35 is relied upon as above.

Lockridge et al. disclose compositions comprising dsNA molecules that are targeted to VEGFR1 and VEGFR2 that are siRNAs that comprise single stranded components that are sense and antisense strands that are 23 nucleotides in length

Art Unit: 1635

each wherein the sense and antisense strands can be connected by a nucleotide or non-nucleotide linker (pg. 3-4, sections 0035-0040). Lockridge et al. disclose the modification of the dsNAs of their invention with 5' end and/or 3' end terminal cap moieties including inverted deoxy abasic or glyceryl moieties and terminal phosphorothioate internucleoside linkage, 2'-O-methyl, 2'-fluoro and 2'-H, dsNAs that comprise 5' terminal phosphate groups on the antisense strand and pharmaceutical compositions comprising the nucleic acids of their invention (pgs. 4-5, sections 0051-0060; pg. 9, sections 0097-0098).

Therefore, Lockridge et al. anticipate the instant invention as set forth in claims 1-3, 11-24, 32 and 35.

13. Claims 1, 3 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. 2001 (Nature, Vol. 411) (Cited on the PTO Form 1449 filed 7/22/2004).

The invention set forth in claims 1, 3 and 35 is outlined above.

Elbashir et al. disclose uGL2 (pg. 496, figure 1b) that is a chemically synthesized siRNA comprised of 21 nucleotide sense and antisense strands that form a 19 bp duplex wherein the duplex comprises ribonucleotides and is formulated in liposomes for delivery to cells *in vitro*, which is reasonably considered to read on formulation in a pharmaceutically acceptable carrier. The siRNA of Elbashir et al. is considered to anticipate the instant claim for the following reasons. As written, claim 1 is drawn to a double stranded nucleic acid molecule comprising a sense and an antisense strand wherein each strand is independently about 19 to about 29 nucleotides in length and

Art Unit: 1635

wherein said antisense strand comprises nucleotide sequence that is complementary to nucleic acid sequence encoding VEGFR1 and VEGFR2 or portions thereof. This language is non-limiting. Therefore, the siRNA disclosed by Elbashir et al. is reasonably considered to comprise an antisense strand that "comprises nucleotide sequence that is complementary to nucleic acid sequence encoding portions of VEGFR1 and 2 because uGL2 comprises a "CCU" in the antisense strand that is complementary to a portion of instant SEQ ID NO: 2275 (disclosed in Table IV of the instant specification as being the target of a dsNA that is homologous to VEGFR1 and VEGFR2) wherein that portion is "GGA".

Therefore, Elbashir et al. anticipate the instant invention as set forth in claims 1, 3 and 35.

14. Claims 1-3, 11-24, 32 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Pavco et al. (US 6,346,398) (Cited on the Form PTO 1449 filed 10/14/2005).

The disclosure of Pavco et al. is applied as prior art for the same reasons set forth with regard to Lockridge et al. above. The invention as set forth in claims 1-3, 11-24, 32 and 35 is relied upon as above.

Pavco et al. disclose the use of a nucleic acid based compound to inhibit the expression of VEGFR1 and VEGFR2 (pg. 2, [0025]; pg. 9, [0083]). Pavco et al. disclose that nucleic acids of their invention are chemically synthesized double stranded nucleic acids (siRNAs) that comprise single stranded sense and antisense strands of 23

Art Unit: 1635

nucleotides in length each wherein the sense and antisense strands can be connected by a nucleotide or non-nucleotide linkers and that the siRNAs contemplated as a nucleic acid of their invention can comprise 5' end and/or 3' end terminal cap moieties including inverted deoxy abasic or glyceryl moieties and terminal phosphorothioate internucleoside linkages, 2'-O-methyl, 2'-fluoro and 2'-H modifications, dsNAs that comprise 5' terminal phosphate groups on the antisense strand and pharmaceutical compositions thereof (pg. 6, [0068] – pg. 9, [0083], pg. 17, [0176] – pg. 19, [0200]).

Therefore, Pavco et al. anticipate the instant invention as set forth in claims 1-3, 11-24, 32 and 35.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-3, 11-24, 32 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (US 6,346,398), Sirois et al. (US 2003/0186920 A1), Fire et al. (WO 99/32619, cited on the Form PTO 1449 filed 7/22/04), Elbashir et al. 2001 (cited on the Form PTO 1449 filed 7/22/04) and Parrish et al. 2000 (cited on the Form PTO 1449 filed 7/22/04).

The invention of the instant claims is drawn to a double stranded nucleic acid molecule comprising a sense and an antisense strand wherein each strand is independently about 19 to about 29 nucleotides in length and wherein said antisense strand comprises nucleotide sequence that is complementary to nucleic acid sequence encoding VEGFR1 and VEGFR2 or portions thereof. Dependent claims 2-3, 11-24, 32 and 35 require that the claimed dsNA molecule comprise or does not comprise ribonucleotides, wherein the sense and antisense strands are connected by a linker that is a nucleotide or non-nucleotide linker, wherein the pyrimidine or purine residues of the sense or antisense strands comprise particular nucleotide modifications or phosphorothioate internucleoside linkages, wherein the sense or antisense strands comprise terminal cap moieties that can be inverted deoxy abasic moieties or glyceryl moieties and to a composition comprising the claimed dsNA and a pharmaceutically acceptable carrier.

Pavco et al. teach nucleic acid molecules that are ribozymes that target homologous regions of flt1 (VEGFR1) and KDR (VEGFR2) mRNA for degradation (col. 14, line 40). Pavco et al. teach that the ribozymes of their invention are chemically synthesized and modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-O-methyl, 2'-F and 2'-H modifications, terminal phosphorothioate internucleoside linkages and a 3'-3' inverted abasic deoxyribose and glycerol moieties at the 3' end (col. 12, line 46- col. 13, line 25; figures 7-8 and legends thereof). Pavco et al. teach that Vegf expression is associated with tumorigenesis and that blocking the interaction between vegf and vegf receptors can inhibit tumor induced neovascularization (cols. 1-3).

Pavco et al. do not teach double stranded nucleic acids that comprise sense and antisense strands that are each independently about 19 to about 29 nucleotides in length wherein the strands are joined by a linker that is a nucleotide or non-nucleotide linker.

Sirois et al. (US 2003/0186920 A1) teach antisense oligonucleotides that are homologous to and that inhibit the expression of both flt-1 (VEGFR1) and flk-1 (VEGFR2) genes (pg. 5, [0047]). Sirois et al. disclose that antisense oligonucleotides are commonly used as research and diagnostic reagents and that they are able to inhibit gene expression with exquisite specificity and are often used by those of skill in the art to elucidate the function of particular genes, to distinguish the functions of various members in a biochemical pathway or are harnessed for therapeutic use (pg. 1, [0008]). Sirois et al. disclose that chemical modification of the antisense

Art Unit: 1635

oligonucleotides of their invention can improve stability and intracellular incorporation (pg. 6, [0059]) and provide an extensive teaching of internucleoside linkage, nucleobase and sugar modifications that can be made to antisense oligonucleotides including phosphorothioate linkages, 2'-F, 2'-O-me and 2'-H (deoxy) wherein the modifications can be 3' terminal or 5' terminal modifications (pgs. 7-8).

Fire et al. teach methods of mediating RNA interference using double stranded RNA to inhibit the expression of a target gene, that the dsRNAs of their invention can be comprised of separate complementary strands and can be joined by a nucleotide or non-nucleotide linker (Abstract, pgs. 6-8).

Elbashir et al. teach that the most effective double stranded RNAs for mediating RNA interference are 19 bp duplex RNAs that are comprised of sense and antisense strands wherein the sense and antisense strands are each independently 21 nucleotides in length (abstract; pg. 6885 *entire*; pg. 6886, col. 2). Elbashir et al. teach that some chemical modification of one or both siRNA strands with 2' deoxy or 2'-O-methyl nucleotides is tolerated in siRNAs that mediate gene inhibition, but that complete substitution abolishes RNA interference (pg. 6881, col. 2). Elbashir et al. teach that siRNAs are valuable reagents for inactivation of gene expression (pg. 6884, col. 2). Elbashir et al. teach that 5' phosphate is required on the target complementary strand (i.e., the antisense strand) of the siRNA duplex for siRNA function (pg. 6886).

Parrish et al. teach RNA interference using double stranded nucleic acids that are comprised of alpha thio nucleotide analogues (see figure 5), reasonably considered here to read on double stranded nucleic acids that comprise no ribonucleotides.

Art Unit: 1635

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to chemically synthesize an siRNA duplex that was 19 bp in length comprised of independent 21 nucleotide sense and antisense strands (as taught by Elbashir et al.) wherein the antisense strand comprised nucleotide sequence complementary to nucleic acid sequence encoding both VEGFR1 and VEGFR2 in order to inactivate the gene expression of VEGFR1 and VEGFR2 to inhibit tumor induced neovascularization (as taught by Pavco et al.) One of skill would have found it obvious to make the siRNA as above wherein the siRNA comprised no ribonucleotides (because it was made of alpha-thio-nucleotides as taught by Parrish et al.), wherein the sense and antisense strands were joined by a linker that was a nucleotide or non-nucleotide linker (as taught by Fire et al.) wherein pyrimidine or purine or the pyrimidine or purine nucleotides in the sense and antisense strands were modified as set forth in claims 13-15 and 18-20 wherein the sense strand or antisense strand included a terminal cap moiety at the 5' or 3' end or both that was an inverted deoxy abasic moiety and wherein the antisense strand comprised a phosphorothioate internucleotide linkage at the 3' end and antisense region were 2'O-methyl wherein the 5' end optionally comprised a phosphate and wherein the siRNA was comprised in a pharmaceutically acceptable carrier because the above pyrimidine, purine, phosphorothioate and terminal inverted abasic deoxy moiety modifications were routine and known in the art (of inhibiting gene expression using nucleic acids) to enhance stability and cellular uptake of inhibitory nucleic acids (e.g., ribozymes and antisense oligonucleotides as taught by Pavco et al. and Sirois et al.), because some chemical

Art Unit: 1635

modification of one or both siRNA strands with 2' deoxy or 2'-O-methyl nucleotides is tolerated in siRNAs that mediate gene inhibition, but that complete substitution abolishes RNA interference and because 5' phosphate is required on the target complementary strand (i.e., the antisense strand) of the siRNA duplex for siRNA function. One of skill would have found it obvious to make the siRNA as above that was comprised in a pharmaceutically acceptable carrier in order to use the siRNA to elucidate the particular function of the VEGFR1 and VEGFR2 genes in tumor induced neovascularization.

One of ordinary skill in the art would have been motivated and expected success in chemically synthesizing an siRNA as above in order to use a nuclease resistant inhibitory nucleic acid with enhanced cellular uptake to study the particular function of the VEGFR1 and VEGFR2 genes in tumor induced neovascularization because the structural features of effective siRNA duplexes were known as taught by Elbashir et al. and because siRNAs that comprised no ribonucleotides, wherein the sense and antisense strands were joined by a linker that was a nucleotide or non-nucleotide linker, wherein pyrimidine or purine or the pyrimidine or purine nucleotides in the sense and antisense strands were modified as set forth in claims 13-15 and 18-20 wherein the sense strand or antisense strand included a terminal cap moiety at the 5' or 3' end or both that was an inverted deoxy abasic moiety and wherein the antisense strand comprised a phosphorothioate internucleotide linkage at the 3' end and antisense region were 2'O-methyl wherein the 5' end optionally comprised a phosphate and wherein the siRNA was comprised in a pharmaceutically acceptable carrier because the

Art Unit: 1635

above pyrimidine, purine, phosphorothioate and terminal inverted abasic deoxy moiety modifications were routine and known in the art (of inhibiting gene expression using nucleic acids) to enhance stability and cellular uptake of inhibitory nucleic acids (e.g., ribozymes and antisense oligonucleotides as taught by Pavco et al. and Sirois et al.), because some chemical modification of one or both siRNA strands with 2' deoxy or 2'-O-methyl nucleotides is tolerated in siRNAs that mediate gene inhibition, but that complete substitution abolishes RNA interference and because 5' phosphate is required on the target complementary strand (i.e., the antisense strand) of the siRNA duplex for siRNA function. One of skill would have been motivated and expected success in chemically synthesizing the siRNA as above that was comprised in a pharmaceutically acceptable carrier in order to use the siRNA to elucidate the particular function of the VEGFR1 and VEGFR2 genes in tumor induced neovascularization.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone


Art Unit: 1635

number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba


JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER